Successful Treatment of Crotalid-Induced Neurotoxicity With a New Polyspecific Crotalid Fab Antivenom

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Received for publication August 7, 1996. Revisions received November 12, 1996, and March 17, 1997. Accepted for publication April 2, 1997.

Study objective: To report the effectiveness of a new polyvalent crotalid antivenom on neurotoxicity associated with North American rattlesnake envenomation. Two syndromes of crotalid-induced neurotoxicity have been reported. In severe envenomation by *Crotalus scutulatus scutulatus* (Mojave rattlesnake), weakness and fasciculations of various muscle groups, including those innervated by cranial nerves, may develop. Occasionally respiratory insufficiency develops. The second neurotoxic effect is myokymia, a type of fasciculation most frequently reported after bites by *Crotalus horridus horridus* (timber rattlesnake) and *Crotalus atrox* (Western diamondback rattlesnake). Conventional polyvalent antivenom is often ineffective in the treatment of venom-induced neurotoxicity.

Methods: We report a case series of three patients envenomated by North American rattlesnakes, one of which was identified as *C scutulatus scutulatus*. All three patients experienced neurotoxicity with weakness, paresthesias, and dramatic fasciculations, along with other signs and symptoms of crotalid venom poisoning.

Results: The administration of a new polyspecific crotalid antivenom made of ovine Fab was successful in immediately and completely reversing neurotoxicity in each of these patients.

Conclusion: We report the use of a new antivenom for North American crotalid envenomation that seems to have efficacy in reversing neurotoxicity associated with these bites.

[Clark RF, Williams SR, Nordt SP, Boyer-Hassen LV: Successful treatment of crotalid-induced neurotoxicity with a new polyspecific crotalid Fab antivenom. *Ann Emerg Med* July 1997;30:54-57.]

INTRODUCTION

Systemic toxicity resulting from crotalid envenomation occurs to varying degrees. Hypotension, pulmonary edema, and cardiovascular collapse have been reported but are rare.[1-3] Other effects, such as neurotoxicity—including a type of fasciculation called myokymia—and gastrointestinal symptoms of nausea and vomiting, may be more common. Although the venom of all species of crotalids contains a neurotoxin, significant neurologic effects in human beings following envenomation are rare. Some species, such as *Crotalus scutulatus scutulatus* (Mojave rattlesnake), possess a neurotoxin that is more likely to cause human toxicity with effects that are often refractory to conventional antivenom therapy. We report the cases of three patients who sustained systemic toxicity after rattlesnake bites. Use of a new investigational antivenom in these patients was associated with rapid, complete resolution of toxicity.

CASE 1

A 53-year-old man was bitten on the right index and middle fingers by a small rattlesnake fitting the description of *Crotalus atrox* (Western diamondback). In the ED, the patient reported swelling and pain at the bite site. He also complained of a metallic taste and exhibited fasciculation of various muscle groups, including the facial muscles and arms. The patient's oral and lingual myokymia rendered his speech unintelligible. Swelling progressed up the right forearm over the next hour. The patient's initial hemoglobin was 16.6 g/dL, platelet count 86,000/mm^3 (normal, 130,000 to 400,000/mm^3), prothrombin time of 11.5 seconds (normal, 9 to 12 seconds), partial thromboplastin time 30 seconds (normal, 25 to 33 seconds), fibrinogen 265 mg/dL (normal, 200 to 400 mg/dL), and fibrin split products less than 250 ng/mL (normal, <250 ng/mL).

The patient was given 12 vials of investigational antivenom as a stabilizing dose.

After administration of antivenom, all systemic symptoms and fasciculations resolved within 15 minutes. One hour after antivenom infusion, the platelet count was 211,000/mm^3. Approximately 12 hours after the infusion all laboratory parameters were normal, with the exception of fibrin split products, which increased to 250 to 500 ng/mL. The patient's condition remained stable until his discharge 36 hours later. Neurotoxicity did not recur.

At follow-up on day 6, the patient demonstrated recurrence of coagulopathy. He was treated with additional antivenom. On follow-up 17 days after the bite, the coagulopathy had resolved except for a fibrin split products concentration of 500 to 1,000 ng/mL. Telephone follow-up revealed no further complications.

CASE 2

A 36 year-old man was bitten on the right middle finger by a small Western diamondback while on a construction site. After physically removing the rattlesnake from his finger, the patient made two incisions at the site with a razor blade and sucked the bite.

In the ED the patient complained of numbness around the mouth and tingling of both hands. Swelling of the entire right arm and significant fasciculations of the fingers on the right hand were also noted. Intravenous lines were placed and fluids administered.

Initial laboratory analyses showed a normal blood count and coagulation parameters, except for fibrinogen (83 mg/dL) and fibrin split products (>1,000 ng/mL).

The infusion of six vials of investigational antivenom was initiated but had to be stopped briefly 40 minutes into the infusion because of an adverse reaction. The patient received two vials of Fab every 6 hours for three additional doses as part of the study. By the end of the final infusion, all laboratory abnormalities had resolved except fibrin split products (>1,000 ng/mL). At the time of the patient's discharge, approximately 36 hours after envenomation, all laboratory values were normal.

Physical examination findings 96 hours after presentation were unremarkable, with no unusual bleeding or pain, and the bite site was healing well. However, prothrombin time was longer than 200 seconds, partial thromboplastin time was longer than 300 seconds, the fibrinogen concentration was less than 50 mg/dL, and the fibrin split products concentration was greater than 1,000 ng/mL. The patient had no phone and could not be reached.

The findings of physical examination 10 days after envenomation were unremarkable, and the patient had no complaints. He again noted no abnormal bleeding or bruising. Laboratory assessment at that time revealed a prothrombin time longer than 200 seconds, fibrinogen concentration less than 50 mg/dL, and fibrin split products concentrations ranging from 250 to 500 ng/mL. Further follow-up was not available.

CASE 3

A previously healthy 43-year-old man was bitten on the right index finger by a Mojave rattlesnake. The patient was a paramedic trained in the identification of venomous snakes. Within 5 minutes of the bite he observed oral and facial

paresthesias. Over the next 30 minutes the patient noted the onset of fasciculations and weakness of the tongue, arms, hands and legs.

On ED arrival 1 hour after envenomation, the patient had edema and tenderness of the bitten finger and the hand and distal forearm, with lymphatic streaking and tenderness to the axilla. Labial dysphasia and dramatic fasciculations of the face, tongue, and all extremities were also noted.

Laboratory parameters were normal except for a platelet count of 112,000/mm^3. The patient was given an initial dose of six vials of investigational antivenom. During the infusion, the patient noted a substantial decrease in the paresthesias. Fasciculations were observed to diminish by an estimated 90%, with subsequent return of normal speech. By the time a second infusion of six vials of antivenom was completed, fasciculations had virtually disappeared.

Over the course of the patient's 36-hour hospitalization, tenderness and edema improved. Platelet count increased to 241,000/mm^3 during the hour following Fab infusion. Follow-up visits 2, 4, and 12 days after discharge showed full resolution of all signs of envenomation.

DISCUSSION

More than 1,200 crotalid bites are reported to US poison centers each year.[4] Although human mortality resulting from these bites is rare, morbidity is frequent.[1,2,5] The most common sequelae of significant crotalid envenomation are cytotoxicity and hemotoxicity.[1-3,5] Other systemic effects are neurotoxicity, commonly manifested as weakness, cranial nerve palsies, slurred speech, and a type of muscle fasciculation referred to as "myokymia."[6-10] Respiratory paralysis is rare.[3,6] Most severe neurotoxic effects are reported after bites by the Mojave rattlesnake and are believed to result from the presence of neurotoxins such as Mojave toxin. However, similar effects follow the bites of other crotalids, possibly as a result of interbreeding among species.[6,11] Rattlesnake neurotoxins such as Mojave toxin are believed to act at the presynaptic terminal of the neuromuscular junction by inhibiting acetylcholine release,[12,13] whereas myokymia is thought to result from an interaction of certain venom components with calcium or calcium binding sites on the nerve membrane.[8]

Systemic neurotoxicity following Mojave rattlesnake bites appears resistant to treatment with conventional polyvalent antivenom, and treatment failure is common.[6] Although the reason for this ineffectiveness is unclear, it may be due to an absence of Mojave toxin or related neurotoxins in the venoms used to produce conventional polyvalent antivenom.[14,15] Venom from four snakes is used in the preparation of the polyvalent product: *C atrox, Crotalus adamanteus* (Eastern diamondback), *Bothrops lanceolatus* (fer-de-lance) and *Crotalus derissus terrificus* (South American rattlesnake). None of these snakes is known to possess significant quantities of Mojave toxin A, which is believed to be the main cause of Mojave rattlesnake–induced toxicity.[16] In vitro studies with the investigational antivenom have shown that it protects mice from *C scutulatus* venom better than the conventional polyvalent antivenom.[17]

In the case of crotalid venom–induced myokymia, our experience and that of others suggests that conventional antivenom is ineffective or extremely slow in reversing this effect.[7,8] Reports in the literature describe resolution of fasciculations 4 to 24 hours or longer after conventional antivenom infusion.[7-8] However, we have seen severe cases of myokymia in children who did not respond to treatment with more than 50 vials of the conventional product. Because this type of neurotoxicity occurs most frequently as a result of bites from snakes such as *C horridus horridus*, the venom of which is not used in the production of the conventional product, the apparent lack of efficacy in treatment with conventional antivenom is not surprising. Our patients, however, experienced reversal of myokymic symptoms within minutes of infusion of the investigational antivenom.

The new antivenom used to treat our patients has several important differences from the conventional antivenom. Although both are polyvalent products, the new antivenom is ovine derived and obtained from the venom of the snakes *C atrox, C adamanteus, C scutulatus scutulatus*, and *Agkistrodon piscivorus* (cottonmouth).[17] After the IgG antibodies to these venoms are isolated, they are subjected to papain digestion and affinity purification before the final product is lyophilized. In laboratory studies, the new antivenom has been demonstrated to be as much as 10 times more potent than the conventional product.[17]

We report the cases of three patients with systemic toxicity manifested as paresthesias and fasciculations. One snake was identified as a Mojave rattlesnake. Each patient was treated with a new polyspecific crotalid investigational antivenom composed of ovine Fab. Although previous reports have documented the ineffectiveness of conventional polyvalent antivenom in the treatment of crotalid-induced neurotoxicity, this new therapy shows promise in the reversal of neurotoxicity. Further data are needed to complete the evaluation of this new therapy.

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Reprint no. **47/1/82606**

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